REMARKS

New Claims 26 and 27

Support for claim 26 can be found in the Specification on p. 5, lines 8-33; p. 6, lines 1-2; and lines 18-24; and p. 7, lines 7-12 and lines 19-31.

Support for claim 27 can be found in the Specification, Examples 1, 3-4, 6-9 and 11-14. No new matter has been added with the addition of these new claims.

Claims Rejections - 35 USC § 112 - Indefiniteness

The Examiner rejected Claims 1-25 under paragraph 2 of §112 as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. See Office Action, p.2. The phrases "characterised in," "the use of," and "is in the lactone form" have been amended to "wherein," "using," and "has a lactone form," respectively, in all claims where such phrases were originally found.

With respect to the phrases "feeding" (claims 4 and 26) and "mobile phase" (claims 4, 7-13, 23-24, and 26), Applicant respectfully submits that one of ordinary skill in the art would readily understand such terms. Feeding is described in the specification on p. 5, lines 25-26 ("....; b) feeding the crude HMG-CoA reductase inhibitor dissolved in the mobile phase; ....").

Further, "feed" and "feeding" are defined in the New Webster's Encyclopedic Dictionary, Random House Value Publishing, Inc., Gramercy Books, 1997, New York, p. 246 as "to supply as for maintenance or operation; to furnish for consumption." One having ordinary skill in the art would thus easily understand that "feeding" a crude inhibitor [onto a column] would mean an act or process of feeding or supplying something [onto a column]. The exact phrase "feed" is also used in literature discussions of displacement chromatography, e.g. G. Guiochon, S.G. Chirazi, and A.M. Katti, in Fundamentals of Preparative and Nonlinear Chromatography" where it designates that "the feed (i.e. sample) is injected in a column (cf. Guiochon et al., page 301). For your convenience, a copy of this reference is attached to this response.

In addition, all cited Examples within the application describe a purification process wherein the sample to be purified is fed onto a column. Therefore, claim 4 has

been amended to include the phrase "onto the chromatography column" in step b) after the words "dissolved in the mobile phase."

Regarding the phrase "mobile phase," Applicant respectfully submits that such a term is readily understood by those with ordinary skill in the art. The specification clearly describes both the characteristics with specific examples (pp. 6-7) and the use (Examples 1-14) of solvent systems that are appropriate for use as the mobile phase in the claimed purification process. Moreover, such a phrase is defined in undergraduate analytical chemistry textbooks in introductory discussions of liquid chromatography systems and has long been used in the field of chromotography to distinguish the movign phase from the stationary phase (see, e.g. B.A. Bidlinger et al., Preparative Liquid Chromatography in Journal of Chromatography, vol. 38, (1987) p. 12). This reference has also been attached to the response, for your convenience.

In light of the above arguments, Applicant respectfully submits that the term "mobile phase" is not indefinite and would be readily understood by one having ordinary skill in the art. Therefore, it is Applicant's position that all claims which contain this term are not indefinite with respect to this term.

Claim Rejections - 35 USC § 101

The Examiner rejected claim 25 under 35 USC § 101 because the claimed invention is directed to non-statutory subject matter – i.e., the "use" of the salt (see Office Action p.3, par. 2). To address this problem claim 25 has been re-written as a process claim.

In summary, claims 1-25 have been amended, to address the problems with indefiniteness raised by the Examiner. Claim 25 has been rewritten as a process claim, thus satisfying the requirements of 35 USC §101. Two new claims, claims 26 and 27, have been added. In the amendments and in new claims 26 and 27, no new subject matter has been added. Applicant therefore respectfully submits that all new and amended claims satisfy the requirements of 35 USC. §§112, par. 2, and 101, and are in condition for allowance.

Claim Rejections - 35 USC § 103(a)

The Examiner has rejected claims 1-25 under 35 U.S.C. § 103(a) as being unpatentable over Haytko et al., for reasons of obviousness. As claimed by the Examiner, "The difference between the process taught in the reference and the claimed process herein lies merely in the variation of purification technique .... which is obvious from the teachings of the prior art absent a showing of unexpected results." See Office Action, p. 4, first par.

First, the Haytko patent claims as novel a preparative HPLC process for achieving (>99.5%) purity of relatively small molecules (HMG-CoA reductase inhibitors) when Haytko admits that such a technique was known for purifying larger molecules such as proteins and "is commonly used for the analytical determinations of compound purity." See Haytko, col. 1 lines 23-25. Thus, the Haytko patent merely represents a scaled up version of a known process (i.e., preparative HPLC techniques compared to analytical HPLC techniques). In contrast, Applicant's claimed invention utilizes a new industrial process for the isolation of HMG-CoA reductase inhibitors involving a different chromatography technique, displacement chromatography, which has not been used to date for purification of HMG-CoA reductase inhibitors. Considering that the principle has been known since the 1940s, and the technique was introduced into practice in the early 1980s (see specification, p. 3, lines 17-20), if it were obvious to use displacement chromatography to purify HMG-CoA reductase inhibitors, themselves known since the 1970s (e.g. compactin has been known since 1975, see US-A-3 983.140), it seems someone would have done so before now.

Second, for HMG-CoA reductase inhibitors, purity is the most important criterion to determine which shall be effective for medical treatment. In particular, since HMG-CoA reductase inhibitor-containing pharmaceutical products are frequently taken on a long-term basis for the treatment or prevention of high plasma cholesterol levels, impurities may accumulate during treatment and thereby cause serious side effects (cf. p. 1, 2nd paragraph of the text of the present application).

In view of this essential criterion, it should be apparent that the skilled person would not contemplate a purification technique which is basically different from the pertinent prior art (cf. Haytko et al.), if a purity level at least as good as conventionally

achieved in the art of HMG-CoA reductase inhibitors could not be expected. This holds true even if a possibly more convenient purification method may thereby be applicable.

It should be further acknowledged that, surprisingly, the ultimate purity level was realized by the present invention on at least as high a level as in the HPLC-based process of Haytko et al. (which chromatographic method was conventionally recognized to rank among the best chromatographic techniques), and even without a crystallization step being still required according to Haytko et al.

And, as stated in MPEP 2141, "Objective evidence or secondary considerations such as unexpected results, commercial success, long-felt need, failure of others, ..." must also be considered and evaluated, when submitted. Here, the desire for highly pure, easily obtained HMG-CoA reductase inhibitors has been an on-going objective of those in the field, yet until the presently claimed invention, no one had thought to try displacement chromatography to achieve that goal. As such, Applicant respectfully submits that this particular replacement of one chromatography method for another is not obvious, within the meaning of 35 USC 103(a).

Third, nothing in Haytko et al. suggests that one should replace analytical HPLC with displacement chromatography as described in the presently claimed invention. As stated in MPEP 2142, p. 2100-121,

> "To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves, or in the knowledge generally available to one of ordinary skill in the art to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference .... must teach or suggest all the claim limitations. *In re Vaeck*, 794 F.2d 488, 20 USPQ2d 1438 (Fed.Cir. 1991).

Haytko et al. does not suggest the presently claimed chromatography method. In addition, the fact that such methodology has been known for a long time yet never used on these compounds before now contradicts that notion that there was suggestion or motivation in the knowledge generally available to lead one of ordinary skill in the art to arrive at Applicant's claimed invention. In addition, as discussed above, in advance it

could not be foreseen that displacement chromatography would work efficiently, let alone that it would provide HMG-CoA compounds of a purity level achievable by HPLC chromatography based methods. Thus, there is no expectation of success for such a substitution of methodologies.

As such, it is respectfully submitted that the Examiner has failed to make a *prima facie* case of obviousness based on Haytko et al. Here, there is motivation or suggestion to try the claimed invention, there is no expectation of success, and the secondary considerations of long felt need (i.e. highly pure inhibitors) and failure of others (i.e. to try displacement chromatography to solve the long felt need) have been addressed and overcome. Thus, Applicant respectfully submits that the Examiner has failed to establish a *prima facie* case of obviousness.

In summary, Applicant has addressed a long felt need in the art, come up with a novel solution to the problem, never before tried by others, and identified a purification methodology that improves upon the existing art. Therefore, Applicant respectfully submits that the claimed invention is not obvious.

CONCLUSION

For the reasons set forth above, it is submitted that all pending claims are in condition for allowance. Reconsideration of the claims and a notice of allowance are therefore requested.

Applicant respectfully requests a two-month extension of time; however, this conditional petition for an additional extension of time is being made in the event that the need for an additional extension has been overlooked. Please pay any fees required for the timely consideration of this application from deposit account number 19-4972. The Examiner is requested to telephone the undersigned if any matters remain outstanding so that they may be resolved expeditiously.

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Version with Markings to Show Changes

In the Claims

1. (amended) A process for obtaining a HMG-CoA reductase inhibitor [(characterised in that] comprising one of the steps in the process of the purification of a crude HMG-CoA reductase [inhibitors] inhibitor which includes displacement chromatography [which] and involves [the use of] using a displacer for displacing the HMG-CoA reductase inhibitor.

2. (amended) A process according to claim 1, [characterised in that] wherein the HMG-CoA reductase inhibitor is selected from the group consisting of mevastatin, pravastatin, lovastatin, simvastatin, fluvastatin or atorvastatin.

3. (amended) A process according to claim 1, [characterised in that] wherein the HMG-CoA reductase inhibitor [is in the lactone form] has a lactone form or is in the form of the acid or the salt thereof.

4. (amended) A process according [any one of claims 1 to 3] to claim 1, [(characterised in that] wherein the displacement chromatography includes the following steps:

a) conditioning a chromatography column with a mobile phase [,];

b) feeding the HMG-CoA reductase inhibitor dissolved in the mobile phase onto the chromatography column[,];

c) introducing the displacer for displacing the HMG-CoA reductase inhibitor from the column[,]; and

d) obtaining the purified HMG-CoA reductase inhibitor.

5. (amended) A process according to claim 4, [characterised in that] wherein the [purified HMG-CoA reductase inhibitor is obtained by] obtaining further comprises:

dl) collecting the fractions[, and];

d2) analyzing the fractions with analytical HPLC; and

d3) pooling the fractions depending on the quality of purity.

6. (amended) A process according to claim 4 [or 5,characterised in that] wherein the displacement chromatography further includes [the subsequent step of]:

e) regenerating the chromatography column by washing the column with alcohol/water mixture to elute the displacer.

7. (amended) A process according to claim 4, [characterised in that] wherein the mobile phase is selected from the group of solvents consisting of water, acetonitrile/water solutions, [or] aqueous solutions of lower alcohols, [as well as bufferred] and buffered dilute solutions of organic, halogenated organic or inorganic acids with alkaline metal cations, with ammonia or with amines.

8. (amended) A process according to claim 4, [characterised in that] wherein the mobile phase is selected from the group of solvents consisting of [any one of] water, [an] acetonitrile/water solutions [or an] and aqueous solutions of lower alcohols.

9. (amended) A process according to claim 4, [characterised in that] wherein the pH of the mobile phase used is between 4.5 and 10.5.

10. (amended) A process according to claim 9, [characterised in that] wherein the pH of the mobile phase used is between 6.5 and 8.

11. (amended) A process according to claim 10, [characterised in that] wherein the pH of the mobile phase used is 7.

12. (amended) A process according to claim 4, [characterised in that] wherein the flow rate of the mobile phase through the chromatographic column is between 1.5 and 30 mL/(min cm^2).

13. (amended) A process according to claim 4, [characterised in that] wherein the flow rate of the mobile phase/displacer mixture through the chromatographic column is between 3 and 15 mL/ (min cm^2) .

14 . (amended) A process according to claim 6, [characterised in that] wherein the stationary phase is regenerated with 20 to 100% aqueous solution of lower alcohols after completed chromatography.

15. (amended) A process according to claim 4,
[(characterised in that)] wherein the stationary phase is a reverse phase.

16. (amended) A process according to claim 15, [characterised in that] wherein the stationary phase is a natural reverse phase [such as] including silica gel with alkyl chains of [a] different lengths.

17. (amended) A process according to claim 15, [characterised in that] wherein the stationary phase is either C-18 or C-8.

18. (amended) A process according to claim 15, [characterised in that] wherein the stationary phase is a synthetic cross-linked polymer matrix.

19. (amended) A process according to claim 18, [characterised in that] wherein the cross-linked polymer matrix is a copolymer of styrene and divinylbenzene.

20. (amended) A process according to claim 4, [characterised in that] wherein the particle size of the stationary phase is between 3 and 20 μm.

21. (amended) A process according to claim 20, [characterised in that] wherein the particle size of the stationary phase is between 7 and 15 μm.

22. (amended) A process according to claim 4, [characterised in that] wherein the displacer is selected from the group consisting of long chain alcohols, long chain carboxylic acids, long chain alkyl ammonium salts, aromatic dicarboxylic acid esters, oxo- and dioxo-alcohols, polyalkylene polyglycol ethers and polyaryl or polyalkylene polyaryl ethers.

23. (amended) A process according to claim 4, [characterized in that] wherein the concentration of the displacer in the mobile phase is between 1 and 35%.

24. (amended) A process according to claim 23, [characterised in that] wherein the concentration of the displacer in the mobile phase is between 2 and 20%.

25. (amended)[(The use of a)] A process according to[any one of claims 1 to 24] claim 1 [for producing a] wherein the HMG-CoA reductase inhibitor obtained by the process[with] has HPLC purity exceeding 99.7%.

26. (new) A process according to claim 2 wherein:

(a) the HMG reductase inhibitor has a lactone form or is in the form of the acid or the salt thereof;

(b) the d1splacement chromatography includes:

(i) conditioning a chromatography column with a mobile phase;

(ii) feeding the HMG-CoA reductase inhibitor dissolved in the mobile phase onto the chromatography column;

(iii) introducing the displacer for displacing the HMG-CoA reductase inhibitor from the column; and

(iv) collecting HMG-CoA reductase inhibitor fractions from the stationary phase and pooling the fractions depending on the quality of purity;

wherein the mobile phase is any one of water, an acetonitrile/water solution or an aqueous solution of lower alcohols;

wherein the pH of the mobile phase used is between 4.5 and 10.5;

wherein the flow rate of the mobile phase through the chromatographic column is between 1.5 and 30 mL/(min cm^2);

wherein the stationary phase is either C-18 or C-8 and the cross-linked polymer matrix of the stationary phase is a copolymer of styrene and divinylbenzene;

wherein the particle size of the stationary phase is between 3 and 20 μm; and

wherein the displacer is selected from the group consisting of long chain alcohols, long chain carboxylic acids, long chain alkyl ammonium salts, aromatic dicarboxylic acid

esters, oxo- and dioxo-alcohols, polyalkylene polyglycol ethers and polyaryl or polyalkylene polyaryl ethers and wherein the concentration of the displacer in the mobile phase is between 1 and 35%.

27. (new) A process according to claim 26 wherein the HMG-CoA reductase inhibitor obtained by the process has HPLC purity exceeding 99.7%.